Long-term hepatitis B surface antigen response after finite doses of ARC-520 or JNJ-3989

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Supplementary appendix

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Supplementary Table 1. Treatment received in the AROHBV1001 study (n=38)

PARTICIPANT ID	NUC-NAÏVE	COHORT	TREATMENT RECEIVED
1	No	3b	JNJ-3989 200mg Q4 week + NUC
2	No	3b	JNJ-3989 200mg Q4 week + NUC
3	No	3b	JNJ-3989 200mg Q4 week + NUC
4	No	3b	JNJ-3989 200mg Q4 week + NUC
5	No	5b	JNJ-3989 400mg Q4 week + NUC
6	No	5b	JNJ-3989 400mg Q4 week + NUC
7	No	6	JNJ-3989 100mg Q2 week + NUC
8	No	6	JNJ-3989 100mg Q2 week + NUC
9	No	6	JNJ-3989 100mg Q2 week + NUC
10	Yes	8	JNJ-3989 300mg Q4 week + NUC
11	Yes	8	JNJ-3989 300mg Q4 week + NUC
12	No	9	JNJ-3989 300mg Q4 week + NUC
13	No	9	JNJ-3989 300mg Q4 week + NUC
14	No	9	JNJ-3989 300mg Q4 week + NUC
15	Yes	10	JNJ-3989 200mg Q1 week + NUC
16	No	2b	JNJ-3989 100mg Q4 week + NUC
17	No	2b	JNJ-3989 100mg Q4 week + NUC
18	No	2b	JNJ-3989 100mg Q4 week + NUC
19	No	2b	JNJ-3989 100mg Q4 week + NUC
20	Yes	3b	JNJ-3989 200mg Q4 week + NUC
21	No	3b	JNJ-3989 200mg Q4 week + NUC
22	No	3b	JNJ-3989 200mg Q4 week + NUC
23	Yes	1b	JNJ-3989 25mg Q4 week + NUC
24	No	1c	JNJ-3989 50mg Q4 week + NUC
25	No	1c	JNJ-3989 50mg Q4 week + NUC
26	No	1c	JNJ-3989 50mg Q4 week + NUC
27	No	1c	JNJ-3989 50mg Q4 week + NUC
28	No	12	JNJ-3989 200mg Q4 week + NUC +JNJ-6379 250mg daily
29	No	12	JNJ-3989 200mg Q4 week + NUC +JNJ-6379 250mg daily
30	Yes	12	JNJ-3989 200mg Q4 week + NUC +JNJ-6379 250mg daily
31	No	12	JNJ-3989 200mg Q4 week + NUC +JNJ-6379 250mg daily
32	No	12	JNJ-3989 200mg Q4 week + NUC +JNJ-6379 250mg daily
33	No	12	JNJ-3989 200mg Q4 week + NUC +JNJ-6379 250mg daily
34	Yes	12	JNJ-3989 200mg Q4 week + NUC +JNJ-6379 250mg daily
35	Yes	12	JNJ-3989 200mg Q4 week + NUC +JNJ-6379 250mg daily
36	No	12	JNJ-3989 200mg Q4 week + NUC +JNJ-6379 250mg daily
37	No	12	JNJ-3989 200mg Q4 week + NUC +JNJ-6379 250mg daily
38	Yes	12	JNJ-3989 200mg Q4 week + NUC +JNJ-6379 250mg daily

Supplementary Table 2. Longitudinal profile of serum qHBsAg in 5 participants who received placebo + NUC

Age	Sex	HBeAg	NUC	NUC duration (years)	Serum qHBsAg (log IU/mL)															
					Day 0	Day 1	Day 15	Day 29	Day 43	Day 57	Day 71	Day 85	Day 113	Day 169	Day 392	36M	42M	48M	60M	72M	Log reduction at LFU
53	M	+	TDF	4.0	3.25	3.2	3.19	3.02	3.19	3.19	3.15	3.1	3.15	3.17	3.02	2.62	2.64	2.52	2.35	2.22	1.03
47	M	+	TDF	4.6	3.26	3.17	3.29	3.28	3.26	3.27	3.26	3.24	3.23	3.22	NA	3.01	2.99	2.91	2.63	2.56	0.70
49	M	-	ETV	1.5	2.56	2.58	2.5	2.58	2.53	2.56	2.52	2.53	2.52	2.5	NA	NA	2.41	2.41	2.30	2.16	0.40
57	M	-	ETV	3.2	2.37	2.45	2.39	2.49	2.39	2.49	2.39	2.48	2.39	2.4	NA	2.25	2.10	2.15	2.05	2.02	0.35
37	F	-	ETV	3.1	3.81	3.85	3.8	3.82	3.76	3.78	3.74	3.83	3.79	3.81	3.83	3.67	3.64	3.83	3.81	3.68	0.13

HBeAg: hepatitis B e antigen, ETV: entecavir, LFU: last follow-up, NA: not available, NUC: nucleoside analogue, qHBsAg: quantitative hepatitis B surface antigen, TDF: tenofovir disoproxil fumarate

HBeAg+ subjects were recruited to participate in Heparc-2003; HBeAg- subjects were recruited to participate in Heparc-2002

Supplementary table 3. HBsAg outcomes at nadir or ≤24 weeks from last dose and at LFU among participants with baseline qHBsAg >100 IU/mL (n=55), comparing 1) siRNA and placebo and 2) ARC-520 and JNJ-3989

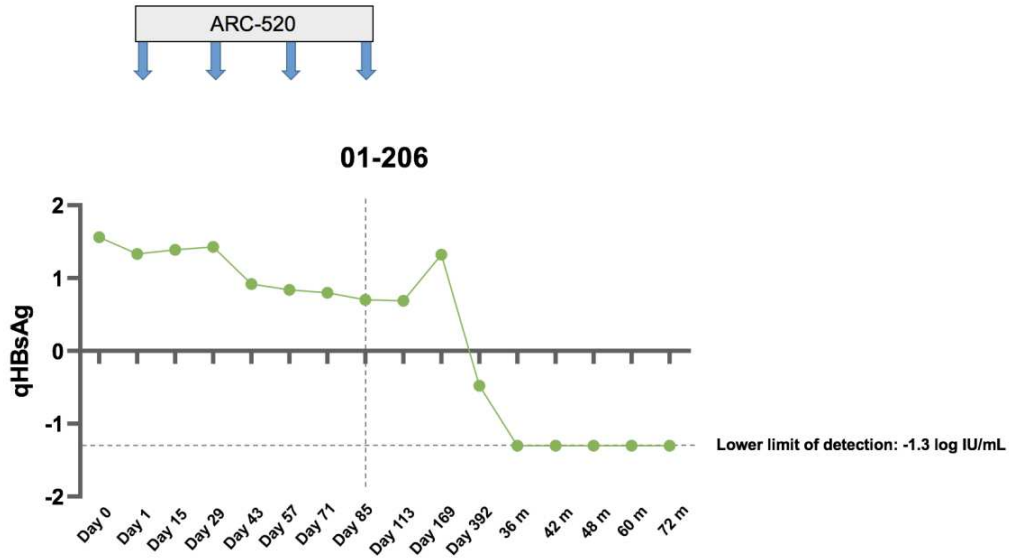
	siRNA (n=50)	ARC-520 (n=13)	JNJ-3989 (n=37)	Placebo (n=5)
HBsAg seroclearance at LFU	0%	0%	0%	0%
qHBsAg log reduction at nadir or ≤24 weeks from last dose	1.61 (SD 0.85)	0.77 (SD 0.49)	1.90 (0.74)	0.53 (SD 0.29)
>1 log reduction at nadir or ≤24 weeks from last dose (%)	72%	15.4%	91.9%	0%
qHBsAg log reduction at LFU	0.82 (SD 0.73)	0.66 (SD 0.52)	0.87 (SD 0.79)	0.52 (SD 0.35)
>1 log reduction at LFU (%)	18%	7.7%	21.6%	20%
<100 IU/mL at LFU (%)	30%	7.7%	35.1%	0%
Annual HBsAg decline	0.21 (SD 0.22)	0.11 (SD 0.09)	0.24 (SD 0.40)	0.08 (SD 0.05)

LFU: last follow-up, NUC: nucleoside analogue, qHBsAg: quantitative hepatitis B surface antigen, siRNA: small interfering RNA

Supplementary Table 4. Mean log reduction of HBsAg at each timepoint

MEAN LOG REDUCTION AT TIMEPOINT	**ARC-520**	**PLACEBO**	**JNJ-3989**
Day 15	0.21	0.01	0.42
Day 29	0.14	0.01	0.66
Day 43	0.24	0.02	0.88
Day 57	0.26	0.01	1.13
Day 71	0.28	0.01	1.41
Day 85	0.28	0.01	1.61
Day 113	0.28	0.03	1.77
Day 169	0.26	0.05	1.64
Day 392	0.27	0.06	1.34
36 months	0.48	0.28	0.85
42 months	0.50	0.29	0.89
48 months	0.61	0.29	1.01
60 months	0.68	0.42	-
72 months	0.86	0.52	-
log reduction at LFU	**0.78**	**0.52**	**0.87**

Supplementary Figure 1. qHBsAg trajectory in a participant who received ARC-520 upon long-term FU

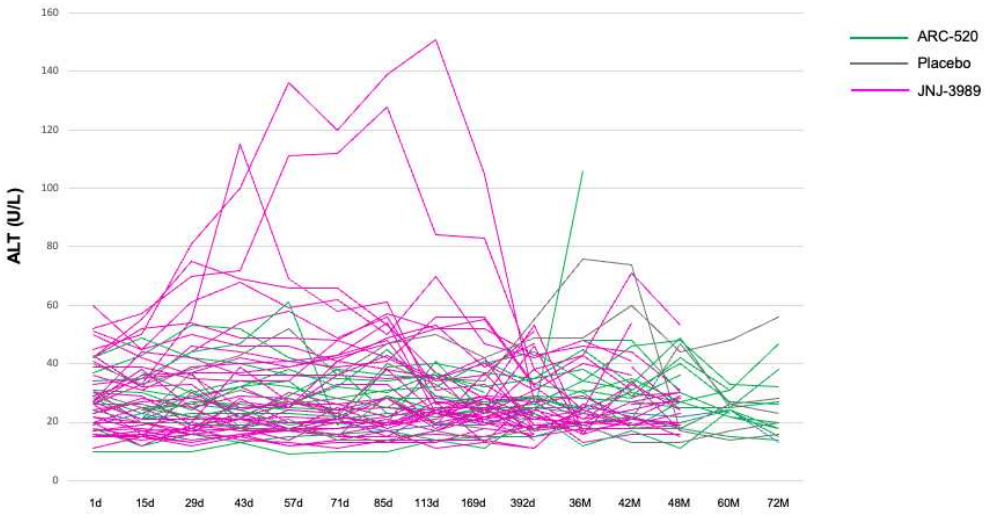


qHBsAg: quantitative hepatitis B surface antigen

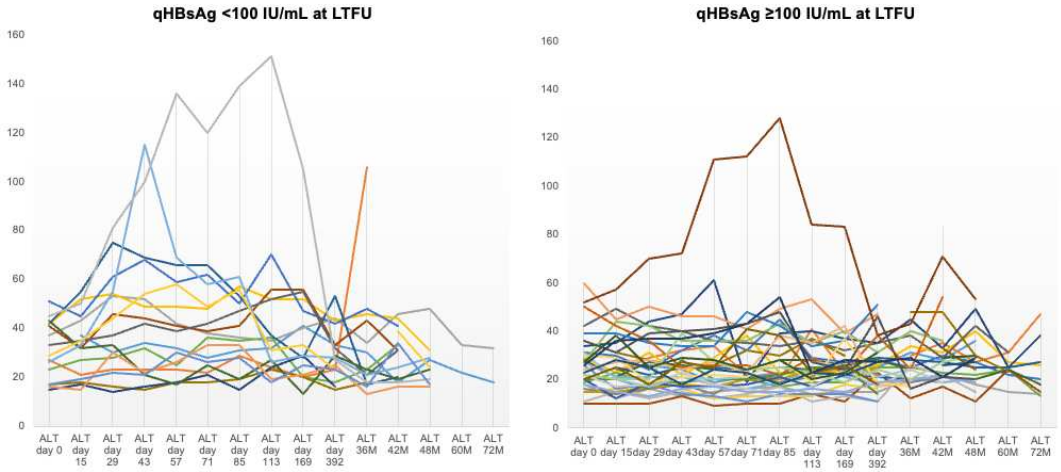
Supplementary Figure 2. Profile of serum alanine aminotransferase (ALT) in (A) all participants stratified by type of treatment received (placebo vs ARC-520 vs JNJ-3989) B) participants who received siRNA, stratified by qHBsAg >100 IU/mL or <100 IU/mL at LFU and (C) participants who received siRNA, stratified by type of siRNA received (ARC-520 vs JNJ-3989)

LFU: last follow-up, qHBsAg: quantitative hepatitis B surface antigen

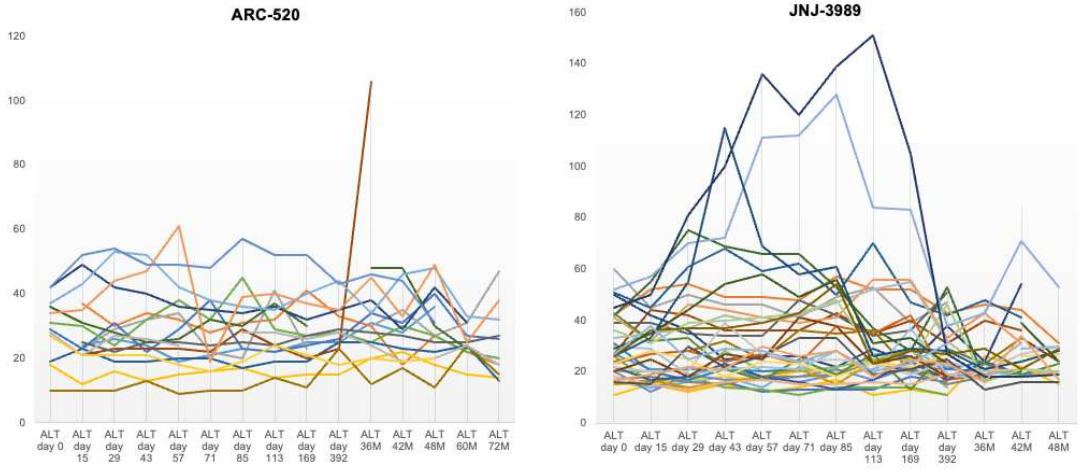
A)



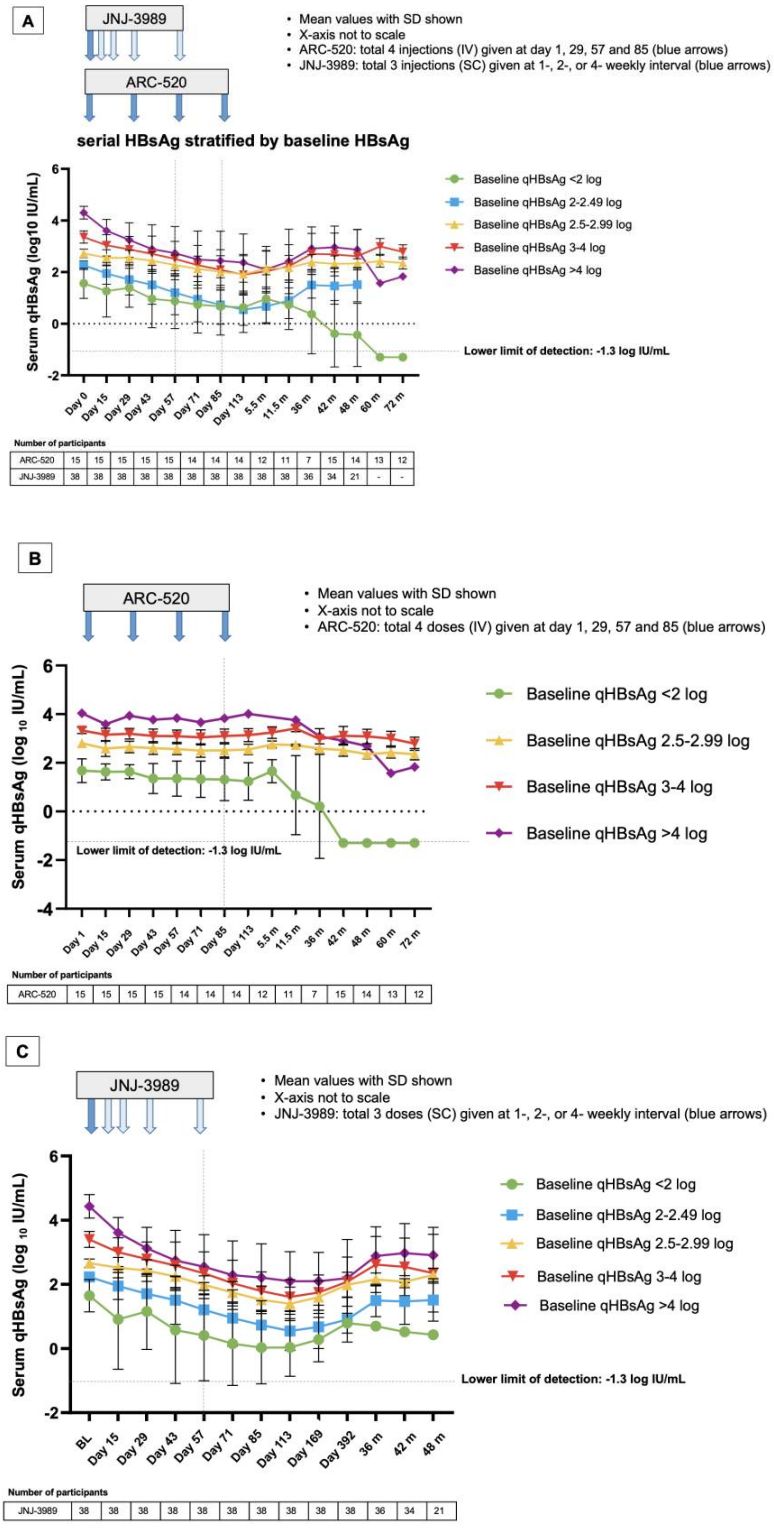
B)



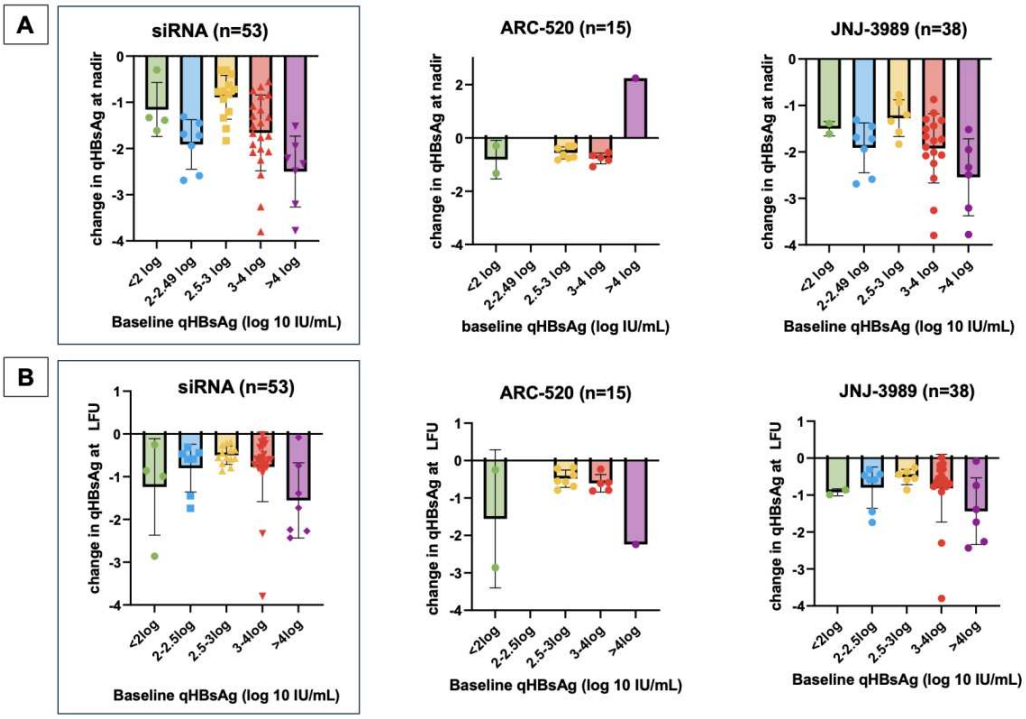
C)


ARC-520
120
100
80
60
40
20
0
ALT day 0
ALT day 15
ALT day 29
ALT day 43
ALT day 57
ALT day 71
ALT day 85
ALT day 113
ALT day 169
ALT day 392
ALT 36M
ALT 42M
ALT 48M
ALT 60M
ALT 72M
JNJ-3989
160
140
120
100
80
60
40
20
0
ALT day 0
ALT day 15
ALT day 29
ALT day 43
ALT day 57
ALT day 71
ALT day 85
ALT day 113
ALT day 169
ALT day 392
ALT 36M
ALT 42M
ALT 48M

Supplementary Figure 3. Kinetics of mean serum HBsAg in 53 participants dosed with (A) siRNA (B) ARC-520 (C) JNJ-3989, stratified by baseline HBsAg levels.
HBsAg: quantitative hepatitis B surface antigen

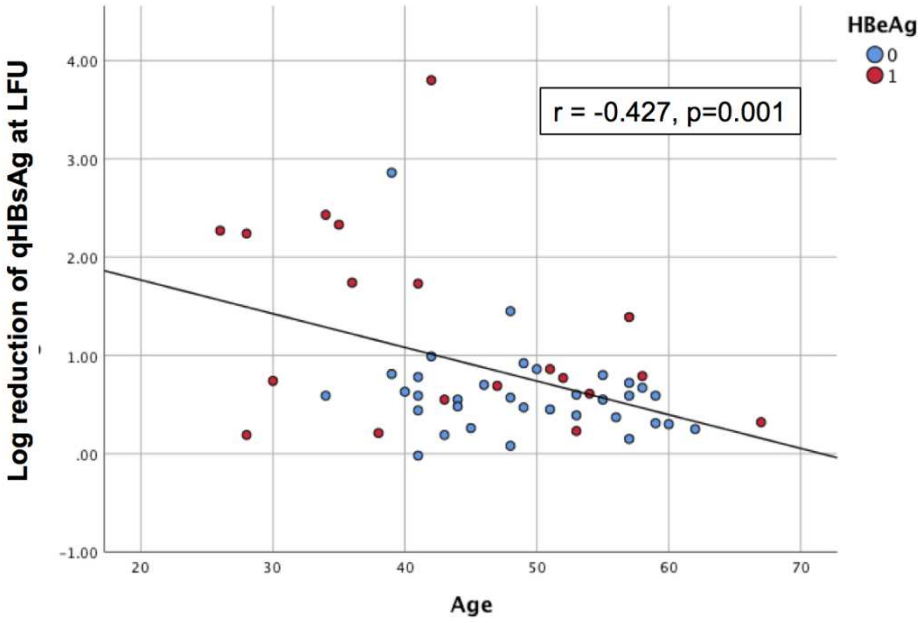


Supplementary Figure 4. Mean change in serum HBsAg (A) at nadir or ≤24 weeks from last dose and (B) at LFU, stratified by baseline qHBsAg levels and type of siRNA received



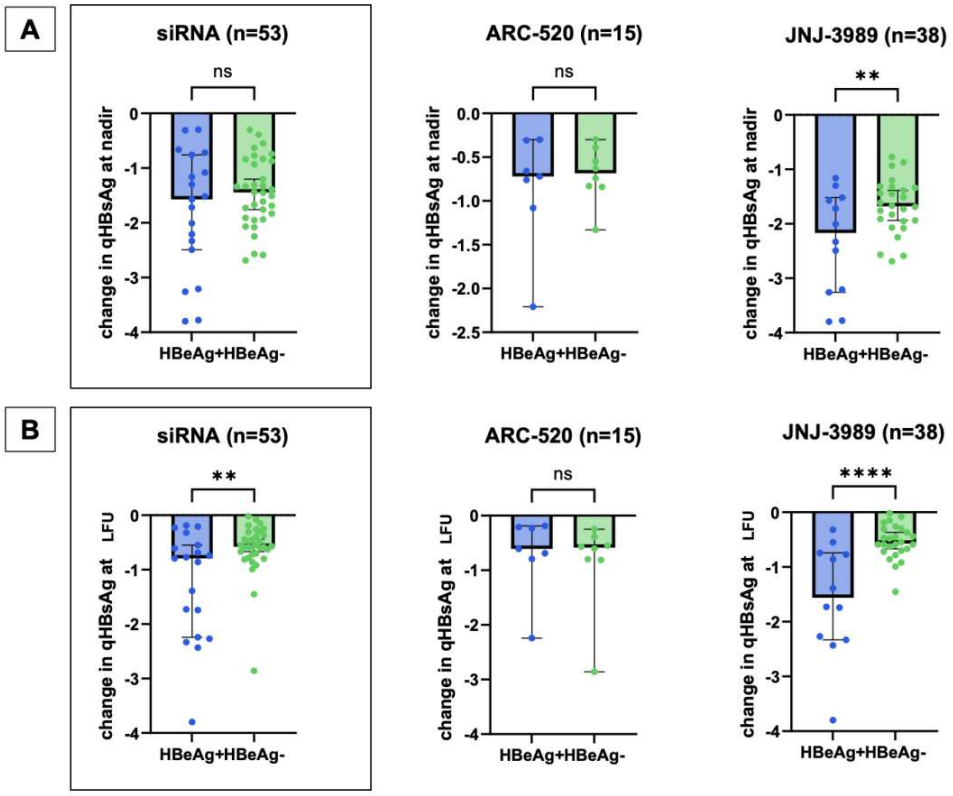
LFU: last follow-up, qHBsAg: quantitative hepatitis B surface antigen

Supplementary Figure 5. Correlation plot between age and qHBsAg log reduction at LFU



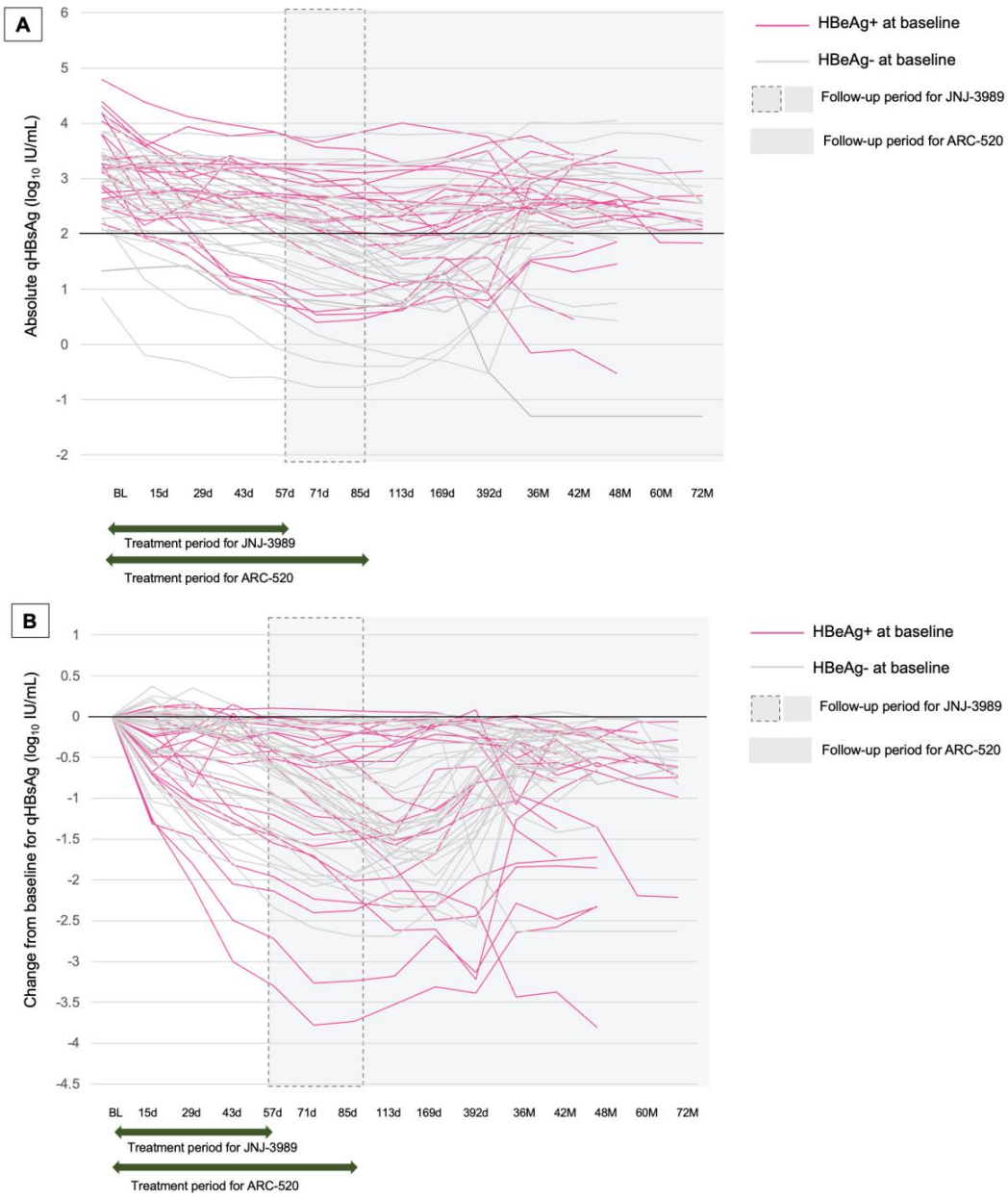
HBeAg: hepatitis B e antigen, LFU: last follow-up, qHBsAg: quantitative hepatitis B surface antigen

Supplementary Figure 6. Mean change in serum HBsAg (A) at nadir or ≤24 weeks from last dose and (B) at LFU, stratified by baseline HBeAg status and type of siRNA received

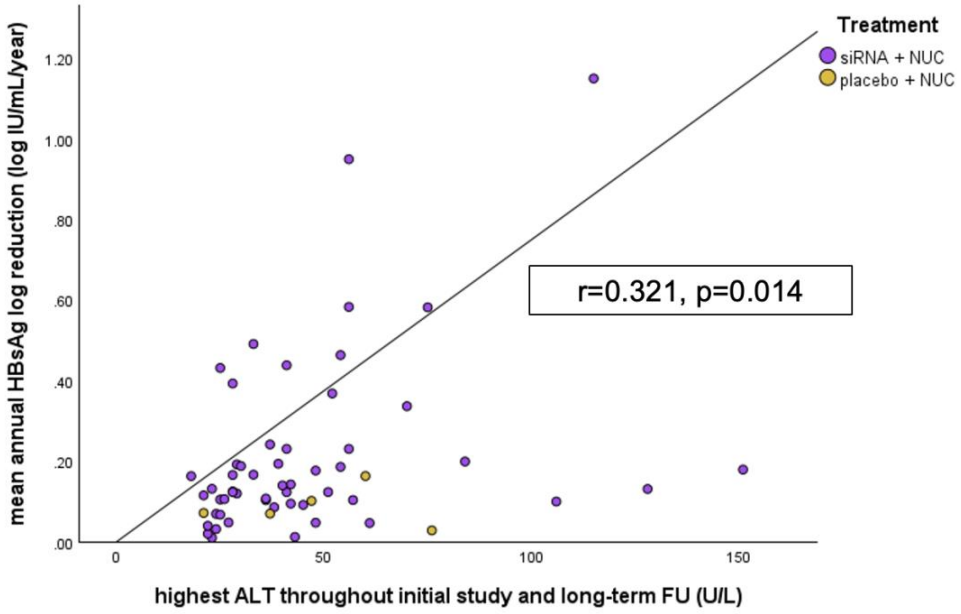
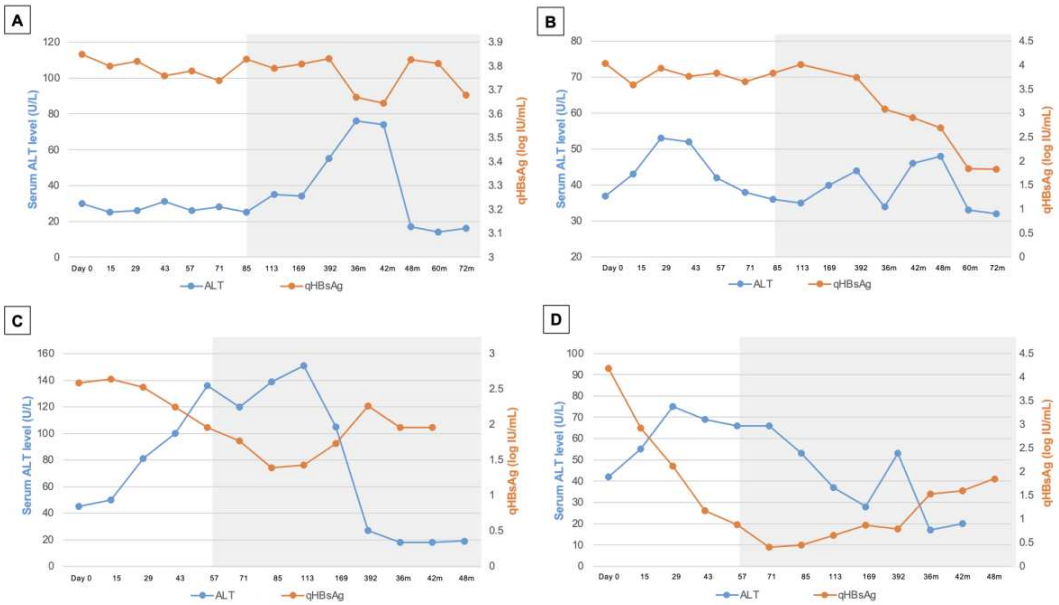


Supplementary Figure 7. Spaghetti plot of qHBsAg trajectories and relative change among participants who received siRNA, stratified by HBeAg status at baseline

A) Absolute qHBsAg levels
B) Relative change of qHBsAg levels



Supplementary Figure 8. Correlation plot between maximum ALT levels observed during initial study and long-term FU with mean annual qHBsAg log reduction at LFU



Supplementary Figure 9. Representative plots of ALT and HBsAg trajectories after siRNA injection in (A & B) 2 subjects who received ARC-520 and (C & D) 2 subjects who received JNJ-3989. The grey area represents post-dosing follow-up period.